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THE PINEAL BODY: A REVIEW.

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Introduction; 1. *Ancient Views of the Pineal Body*; 2. *Comparative Anatomy and Development*; 3. *Comparative Histology*; 4. *Clinico-Pathological*; 5. *Experimental*; 6. *General Discussion*; 7. *Conclusions*; 8. *References.*

INTRODUCTION.

THERE appears to be no really satisfactory review in the English language dealing with all aspects of the pineal body. Histological, experimental, and clinico-pathological evidence has been accumulating during the past few years—and even months—which suggests that the question is no longer, "Has the mammalian pineal body any functions?" but rather, "What are its functions, and how does it functionate?"

In this review my object is to so present the subject that we may learn by it the extent and the limitations of our present knowledge of pineal physiology, and may also learn in what directions this may be increased. In the clinico-pathological section I am not at all concerned with the purely intracranial signs and symptoms of pineal tumours, but only with the metabolic symptoms shown by about 10 per cent. of the recorded 65 cases.

1. ANCIENT VIEWS OF THE PINEAL BODY.

The mammalian epiphysis was known at any rate in pre-Galenic ages; and Studnička[5] mentions that Faivre[2] (1857) claims that Galen[1] and also Oribas knew of the existence of brain-sand in the human pineal body. The pre-Galenic teaching was that the pineal body acts towards the fourth ventricle in the same sort of way in which the pylorus acts towards the stomach, viz., that its function is to allow only the proper amount of the vital spirits to pass from the third to the fourth ventricle. Galen[1] refuted this ancient teaching: he writes of the pineal as a gland, similar to the other glands of the body. The statement is made by Paul Seigneur,[6] in his recent thesis, that Galen looked on the pineal as a gland which furnishes a secretion. I have failed to verify the latter part of this statement from a study of any of the three editions of Galen to which I have had access.* But if Galen really did teach this, his foresight was truly remarkable. Seigneur states that Magendie revived the pre-Galenic teaching, and held that the pineal acts as a pad whose function is to open and close the Sylvian aquæduct. There is no need to refer in detail to the fanciful guesswork of Descartes (1649). It is stated by Faivre[2] (1854) that in 1680 Duverney announced to the Academy of Sciences that the dog has no pineal: this teaching was accepted by Samuel Collins in his "System of Anatomy," and also by Camper, but was refuted by Soemmering, Gisbert, and Jacob Wolff.

We can conveniently divide the history of the study of the pineal body into the following eras: (1) the pre-Galenic; (2) the Galenic; (3) the period of the dark ages ending about A.D. 1824; (4) an era of twilight, beginning in 1824, when the epiphysis of *Petromyzonts* was studied more or less by Serres (1824), Schlemm and D'Alton (1838), Johannes Müller (1839), Siebold and Stannius (1854), and Mayer (1864); and, finally (5) the modern era which began with the careful comparative histological studies by Faivre[2] (1854) of the mammalian, avian, and reptilian epiphysis.

It is said that the early history of the epiphysis is given by (1) Longet (1847), (2) Faivre[2] (1857 paper), (3) Legros[3] (1873), (4) Peytoureau[4] (1886-87), and (5) by Duval (1888). The references to Longet and Duval are given by Studnička.[5]

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* Apparently Seigneur relies here on the thesis of Peytoureau;[4] for in his bibliography he gives two references to Galen, and in each case adds "cit. par Peytoureau." I have to thank Mr Victor Plarr, the Librarian of the Royal College of Surgeons, London, for his kind help in translating passages from Galen.

2. COMPARATIVE ANATOMY AND DEVELOPMENT.

Although several observers studied the comparative anatomy of the epiphysis of lower vertebrates during the second and third quarters of the nineteenth century, the first really notable discovery appears to have been made by Leydig[7] in 1872: he then described a parietal sense-organ in *Anguis* and *Lacerta*, which he called "the frontal organ": he stated that there was no evidence as to its function. In 1882 Ahlborn[9] suggested that the parietal organ of Leydig is to be compared with the unpaired eye of *Amphioxus* and of *Tunicata*. In the same year Rabl-Rückhard[8] suggested the homology of this organ with the median eye of *Arthropoda*; and in 1884 he drew attention to the parietal foramen of fossil reptiles. These researches were soon followed by numerous studies of the development of the epiphysis, viz., those of de Graaf[10] (1886), Baldwin Spencer[11] (1886), Beard[12] (1888), Francotte[13] (1888), Béraneck[14] (1892, '93), C. Hill[15] (1891, '94), Dendy[16] (1899, 1907, 1911), and others. The most recent studies are those of Terry[17] (1910) in *Teleosts*, and J. Warren[18] (1911) in *Reptiles*.

So far as is at present known, an epiphysis is present in all vertebrates, with the exception of *Myxinoids* (Studnička), *Torpedo ocellata* (D'Erchia[19]), and *T. marmorata* (Studnička[5]), and all the *Crocodilia* (Sorenson,[20] Voeltzkow[21]). Not only is this true for the adults of these forms, but even in their ontogeny no trace of an epiphysis has been found—at any rate in the *Crocodilia*. In mammals the epiphysis appears as a single outgrowth or evagination of the hinder end of the roof-plate of the diencephalon. In lower vertebrates usually two epiphyses are seen at a very early stage of development: these are usually strictly median in position: the anterior one is developed in the anterior part of the diencephalic roof, and the hinder one in its posterior part. In most forms the anterior (epiphysis 1) becomes the pineal "eye" of those few forms which possess a recognisable one, whereas the hinder (epiphysis 2) becomes the pineal body. In other forms, the anterior either disappears or becomes fused with the hinder. It was formerly taught that the pineal eye is formed from the distal end of the epiphysis, from which it is constricted off; but few modern writers accept this view. Most authorities hold that two epiphysial evaginations occur: of these, the anterior is the future pineal sense-organ or eye, the posterior the "epiphysis." But some observers argue for a primitive bilateral origin of the pineal eye and epiphysis (pineal organ), so that they were originally paired structures. Thus, Gaskell[22] maintained that the pineal sense-organs of the *Ammocœtes* of *Petromyzon* were paired organs. Dendy[16] states that in *Petromyzonts* the hinder epiphysis is much more developed than the anterior, and is actually median in position; he found that in *Geotria australis* (the New Zealand fresh-water lamprey) the anterior organ lies a little to the left of the median line: the posterior becomes the pineal eye and is connected by the "pineal nerve" with the right habenular ganglion.

Locy[23] (1893, '94) described in the Selachian *Acanthias vulgaris* two pairs of symmetrically developed "accessory optic vesicles," behind the optic vesicles, on the open neural plate. He held that these are serially homologous with the optic vesicles: he derives the pineal pair from the more anterior pair of these accessory vesicles. His observations have, however, never been confirmed on embryos of this easily accessible Selachian. In 1891 C. Hill[15] found in *Teleosts* and in the Ganoid *Amia* right and left primary epiphysial outgrowths. Dendy[16] found (1899) that, in that very primitive type of reptiles *Sphenodon*, the left epiphysial vesicle becomes the parietal eye. Béraneck[14] described right and left epiphysial outgrowths in *Lacertilia*, and strenuously maintained the doctrine of the individuality of the pineal eye. John Cameron[24] showed that, in the chick, at about the fiftieth hour of incubation the epiphyses appear as bilateral outgrowths from the roof of the diencephalon, the left being the larger: by the sixtieth hour the two outgrowths have coalesced to form the single unpaired outgrowth. He points out that the transitory appearance of the bilateral condition explains why it had been previously overlooked. He found the same state of affairs in *Amphibia*. I note, however, that in very early stages in reptiles Warren[18] found the two epiphyses strictly median in position from the first. It is only right to mention here that Cameron,[24] who strongly champions the "primitively bilateral origin" hypothesis, has shown in *Teleosts*, *Amphibia*, *Birds*, and *Man*, nerve-fibres passing from the ganglion habenulæ of one side to epiphysial elements on the opposite side, forming a true decussation in the superior (habenular) commissure. Dendy[16] admitted candidly in 1899 that at present it is not possible to explain why these two organs (epiphysial vesicles) should so persistently tend to alter their positions from the primitive transverse to the sagittal plane. He draws attention to the fact that in the Devonian fossil fish *Titanichthys* there are paired parasagittal parietal foramina present.

The variations of the vertebrate epiphysis are very great. For the following compilation I am indebted especially to Studnička's monumental paper,[5] and to Dendy's excellent one[16] on the pineal gland in "Science Progress."

1. *Adult Elasmobranchs.*—In *Spinax niger* the epiphysis is a median, unpaired body in the form of a long slender tube which passes forwards and ends in a terminal enlargement lodged in the cartilaginous roof of the cranium. Studnička describes its walls as containing numerous modified columnar ependymal cells whose free extremities project slightly into the lumen of the organ.

2. *Ganoids.*—In *Acipenser* (sturgeon) the structure resembles that of Elasmobranchs.

3. *Teleosts.*—The same thing is true here also; but the proximal part is much shorter, and its terminal vesicle is usually larger, and may have its wall much folded. C. Hill[15] describes, in the Salmon numerous cells, resembling ganglion cells, in the wall of the vesicle.

4. *Amphibia.* — (*a*) Urodela — have a single pineal organ: it apparently represents the proximal part of the stalk of a more fully developed pineal organ, such as occurs in fishes. (*b*) Anura—the

pineal organ is single, but has both a proximal and a distal vesicular part. The former contains the usual modified ependymal cells with their free ends projecting into its cavity.

5. *Reptilia.*—Of existing forms, only *Sphenodon* and *Lacertilia* have a pineal eye: but a parietal foramen was present in many extinct forms. In *Ophidia* the pineal organ is a solid, very vascular body, and resembles that of birds and mammals.

6. *Aves.*—The epiphysis may be tubular, follicular, or solid; and it is usually connected with the brain by a hollow or a solid stalk. In *Meleagris* there are vast numbers of small follicles, lined by ependymal epithelium, and separated from one another by vascular connective-tissue; and Studnička has demonstrated the presence of ependymal cells with their free extremities projecting into the cavities of the follicles.

7. *Mammalia.*—The pineal body usually resembles that of birds, and is very vascular; but there are great variations, sometimes even in closely related forms: the recent studies [54] of Cutore (1912) show this well: thus, he finds great macroscopic differences between the pineals of *Macacus* and *Cercopithecus.* Again, the study by Jordan [57] (1911) of the epiphysis of the Virginian Opossum shows a very primitive type quite reptilian in character.

In summing up this section, we may say that it is clear that the morphology of the epiphysial organs is not yet fully understood, and that it presents problems of great difficulty.

3. Comparative Histology.

[I have made free use of the monographs of Mdlle. Dimitrova [50] and of Studnička [5] in the following section: to several papers I have not had access, but in these instances I have been at pains to compare as many abstracts of these as I could find. Dimitrova gives an excellent historical summary up to 1901; and Studnička summarises the literature of the histology of the mammalian pineal under six headings, viz.: (1) Connective-tissue framework; (2) Ependyma; (3) Parenchyma—neuroglia; (4) Nerve-bundles in the epiphysis; (5) Ganglion-cells (?); (6) Pigment in the epiphysis.]

v. Kölliker [25] (1850) described small round cells, multipolar nerve-cells, compact bundles of cells, and a few nerve-fibres.

Faivre [2] (1854) was apparently the first observer who made a careful comparative histological study of the pineal body. [Curiously, this paper is not mentioned by Dimitrova, though she quotes Faivre's later paper of 1857—a paper to which I have not had access.] Faivre studied the pineal of Man, horse, guinea-pig, dog, ox, rabbit, pig, the hen, turkey, turtle-dove, and the tortoise; unfortunately he gives no figures. He refutes the teaching that the parenchyma is composed of grey matter analogous to the cortical substance: superficial examination, even, shows the error of this; he quotes Valentin ("Neurologie," p. 222) that the pineal has a striking histological resemblance to the pituitary. Faivre describes the pineal of Man as formed of three elements, viz., (1) the fibro-vascular envelope, which sends many prolongations into the interior, (2) the globular or nuclear parenchyma, (3) the brain-sand or inorganic material. Of these, the parenchyma is the most important. The parenchyma is formed essentially of a large quantity of "globules"; these, full of grains ("grenus") in their interior, are generally elliptical with irregular borders; their diameter averages ·015 mm. He says that these globules do not call to mind the structure of the histological elements of the nervous system, and that comparative histology shows that the "globules" are the nuclei of the cells. I interpret these descriptions to mean that Faivre recognised that the nuclei of the parenchymal pineal cells of Man contain granules; if this be correct, he was the first observer to make this discovery. [I find that practically all modern writers appear to have overlooked this earlier paper of Faivre, probably because Dimitrova has no mention of it; and it is certain that everyone who wishes to learn about pineal histology consults her paper's historical summary.] It is of interest to note that Faivre found the "globules" were smaller in a girl of 3 years than in a woman of 60. In the horse he found throughout the parenchyma a large number of small black granules ("grains") endowed with remarkable Brownian movement. Its globules are much larger than Man's, viz., ·02 mm.; some differences between the pineals of the horse and of Man are mentioned.

He notes that the guinea-pig's pineal is easily missed; it is very small (2 mm. length), slender, and easily torn out in preparation; its ovoid granules are ·012 to ·006 mm. in diameter, *i.e.*, slightly smaller than in Man, and are full of blackish "granulations": Faivre found also small grains of calcium phosphate, and of concretions whose nature he failed to determine. The dog's pineal resembles Man's; its globules are very small (·004 to ·006 mm. in diameter). The hen's pineal has the ordinary globular structure: the small "grains" are rounded, and are from ·001 to ·002 mm. in diameter: their contents are sometimes granular, but more often they appear to be surrounded by a whitish zone which seems to be the cell of which they are the nucleus. Other birds resemble the hen, both as to the position and structure of the pineal. At the end of his paper Faivre states that in all the animals which he examined, viz., mammals, birds, and reptiles, he got the same results. He appears, then, to have been the first to establish two facts which are now recognised by modern histologists, viz., (1) that the nuclei of the parenchymal pineal cells contain granules, and (2) that there are certain histological differences in the pineals of the child and of the adult.

In his second paper (1857) he is stated by Dimitrova [50] to have "described round the gland a connective-tissue sheath coming from the choroid plexus, and fibro-vascular septa which penetrate into its thickness and divide it into a large number of cavities. These are occupied by the special elements, which are distinct from those which enter into the composition of the nervous system but approach the nerve-elements of invertebrata and of embryos. In Man and the horse Faivre has found nerve-elements in the pineal peduncles; he finds also concretions, which are, he thinks, due to the rich vascularity of the organ."

Lockhart Clark[26] (1861) found nerve-fibres, nuclei, and brain-sand, but no nerve-cells. He writes: "Its reticular structure bears a decided resemblance to the epithelium of the olfactory mucous membrane and still more to what I have described elsewhere as the fourth layer of the olfactory bulb in the sheep, and particularly in the cat."

Luys[27] (1865) looked on the pineal as formed of grey matter and of nerve-fibres which are connected with various regions of the brain.

Leydig[7] (1866) says that the structure of the mammalian pineal, especially of the mouse, resembles that of the pituitary body of reptiles, with certain small differences, however.

Krause[28] (1868) described nerve-fibres with a double contour.

Stiéda[29] (1869) studied the pineal of birds and mammals, and described an anastomosis of the processes of the pineal cells; and he found nuclei in the reticulum.

Bizzozero[30] (1871) described two sorts of cells; and he appears to have been one of the first to discover—as many observers have since found—that there are certain differences between the cells of the pineal of newly-born animals and those of adults. He found often a yellowish or brownish pigment in the connective-tissue cells; he found no true septa, but only irregular trabeculæ.

Meynert[31] (1871) looked on the pineal as a nerve-ganglion.

Hagemann[32] (1871-72) studied fishes, birds, and mammals; he described two kinds of epithelial cells, viz., round and fusiform; also bipolar and multipolar nerve-cells. Thus he regarded the pineal body as composed of a mixture of epithelial cells and nerve-elements.

Cruveilhier[33] (1877) found (1) pale rounded cells without processes, (2) multipolar cells, (3) a small number of nerve-cells, and (4) a multitude of calcareous concretions.

Mihalkovicz[34] (1877) says that developmental studies show that the pineal cells are not lymphatic corpuscles; they are in their origin homologous with the epithelial elements of the cerebral ventricles.

Schwalbe[35] (1881) held that there is a striking resemblance between the pineal cells and those of lymphatic corpuscles; but he regarded them as, developmentally, modified epithelial cells.

Cionini[36] (1885-86) demonstrated—apparently for the first time—the presence of neuroglial elements; the few nerve-fibres met with belong to the vessels.

Darkschewitsch[37] (1886), who studied the frog, rabbit, dog, ape, and human fœtus, describes and figures in the dog medullated fibres connecting the pineal and the posterior commissure. He describes great abundance of nerve-fibres. He used Weigert's hæmatoxylin method.

Henle[38] (1887) looked on the pineal as a lymphatic ganglion: he described its parenchyma as containing two kinds of cells, viz., (1) round cells which resemble lymph corpuscles or leucocytes (but are a little larger), and (2) angular cells provided with points.

ELLENBERGER [39] (1887) describes the horse's pineal as very vascular; under a low power it resembles in structure a lymphatic gland. Only rarely did he find nerve-fibres in the pineal: they are continued into its stalk, but he failed to trace them to their termination.

FLESCH [40] (1888) studied the pineal of horse, sheep, pig, dog, bat, and Man; he found brain-sand only in Man. He denied that the pineal of mammals is a rudimentary organ, and regarded it as an epithelial organ: he found nerve-fibres. He points out that the size of the pineal bears no relationship to the size of the brain; thus the small-brained sheep has a relatively large pineal. He argued that the mammalian pineal is physiologically active, because (1) it contains nerves, (2) is very vascular, (3) its specific cells contain pigment-granules. He held that it was probably a secretory organ. He suggests that it may also contain a heat-regulating centre.

EDINGER [41] (1889) says that in higher mammals the pineal is formed of neuroglial cells, and that nerve-elements are absent.

CHAUVEAU [42] (1889) finds in the connective-tissue, vesicles filled with polyhedral cells.

MINGAZZINI [43] (1889) claimed that the pineal elements resemble lymphatic corpuscles.

SOURY [44] (1889) found a substance, resembling adenoid tissue, packing the spaces of the fine network and cellular elements.

WEIGERT [45] (1895), working by his own method, described the pineal cells as bound together by an abundant, but loose, network of large neuroglial fibres.

CAJAL [46] (1895) found sympathetic nerves penetrating the pineal body with its vessels: their axons form a rich interstitial plexus: the terminal nerve-twigs are situated on the external side of the glandular cells, but do not penetrate into their protoplasm; this relationship is like that found by several authors for other secreting glands.

GALEOTTI [47] (1896-97) argues for a secretory function of the pineal; and he appears to have been the first to attempt to show how this secretory process is carried out. He worked on the adult rabbit, also on an embryo white rat, of 14 mm. length, and on lower vertebrates. In the rabbit he described the parenchymal cells as irregularly disposed: their nucleus is oval, and is surrounded by a little granular protoplasm: pigment is often contained in the cells. Pigment-granules are found in both the cytoplasm and the nucleus of the cells: sometimes they are accumulated in the cytoplasm in notable quantity. Galeotti held that not only do the pineal cells elaborate pigment, but also, by different mechanisms, a product of secretion in whose formation the nucleus and nucleolus participate. Dimitrova [50] (to whose account chiefly I have had to trust) holds that these conclusions are unwarranted by Galeotti's observations. I find the statement is made by Foà [81] (1912) that Galeotti, applying his own elective coloration method, found abundance of "secretory" granules in the epiphysis of *Scyllium canicula*, *Leuciscus cephalus*, *Rana esculenta*, and in a nine days' embryo of *Gallus*; whereas he failed to find them in *Anguilla vulgaris*, *Spelerpes fuscus*, *Triton cristatus*, and *Proteus anguineus*.

Lord[48] (1899) described the parenchyma of the human pineal as formed of small stellate cells resembling those of adenoid tissue, and of pale elements of variable shape.

Nicolas[49] (1900) found striped muscle-fibres in the pineal of the ox and calf, chiefly in the distal part: they may be superficial or deep, are very few in number, and easily found when large. Their size varies from 66 to 100 μ in length by 4 to 6 μ in breadth: they are accompanied by neuroglial fibres: and Nicolas never saw any connection of these muscle-fibres with vessels. His pupil, Mdlle. Dimitrova, confirmed his results, in the following year, in all the six pineals of ox and calf which she examined. But no one else has since that time found striped muscle-fibres in any normal mammal.

Dimitrova[50] (1901) studied the pineals of many mammals, young and old, by many methods; these included Man, ox, calf, sheep, horse, dog, and cat: all her observations were made on fresh glands: even her human material was never more than five hours old. She is the great champion of the essentially neuroglial nature of the mammalian pineal. She discusses the meaning of the intra-protoplasmic granules and the intra-nuclear droplets which she found. She writes: "If the presence of granules is sufficient to prove a glandular function, then the pineal cells are in the highest degree glandular." But she admits that her observations do not admit of a definite answer to the question of an internal secretion. She found that calcareous concretions were common and large in Man and the ox; pigment was specially frequent in the horse: it is found in the parenchymal cells and, more often, in the connective-tissue cells. Her conclusions may be summarised thus: (1) The pineal is composed essentially of neuroglial elements; (2) cavities exist in the pineals of ox, calf, sheep, and dog: they resemble thyroid vesicles, or the vesicles in the anterior lobe of the pituitary (she suggests that they represent vestiges of the primitive budding); (3) she found, in young cats only, some cells which are independent of the neuroglial cells: their significance is doubtful, but they resemble those which Cajal and Retzius have described as "sympathetic": she suggests that they are developing neuroglial elements; (4) she has never seen fibrils, of clearly nervous appearance, except in young animals: they could not be recognised in adults in the midst of the innumerable fibrils impregnated by the chromate of silver.

Anglade and Duclos[51] (1908-09) found neuroglia constantly in the human pineal: sometimes it appears to form an accessory support by connection with the connective-tissue: sometimes the septa are formed in great part by neuroglial elements: in the alveoli there are always neuroglial cells and fibres, but there are also probably cellular elements of another nature.

Sarteschi[52] (1910), whose very important paper I know only by several abstracts, studied the pineal of birds and mammals (guinea-pig, rabbit, sheep, pig, cat, dog, ox, horse, and Man) both young and old. The pineal of the newly-born child differs from that of the adult. A pronounced glandular structure exists especially in birds; but only in certain very young mammals—rabbit and guinea-pig—is it very definite: in the sheep, ox, horse, dog, and cat, secretory processes are not so evident, but Sarteschi holds that they cannot be denied. In the course of growth regressive changes occur, and these can be demonstrated histologically. The pineal of birds differs from that of mammals, and has a characteristic aspect. In *Gallus* glandular and neuroglial elements are found: the nuclei of the glandular cells are rich in fuchsinophile granules. The organ is divided by the connective-tissue septa into a large number of multilocular cavities, often irregular, in the central part of which is often seen a clear lacunar space, more or less large, in relation to which the glandular cells frequently take a radial disposition. In the interior of this space one sees numerous transparent spherules whose limiting membrane alone stands out prominently. Sometimes between the spherules there are irregular granular masses, at other times groups of elements exactly like glandular elements; the cell-body of these glandular elements has a spongy structure. The neuroglial elements appear specially evident about the capsule, and sometimes along the septa. In the pineal of the guinea-pig and rabbit most of the cells are polygonal, and have a spongy protoplasm; other cells, which present similar characteristics, are distinguished by their swollen appearance: and a clear space, full of liquid, is formed in the cell-body. One often sees spheres of various sizes, either isolated or grouped. In very young rabbits the pineal cells have abundant protoplasm, with a nucleus rich in fuchsinophile granules; in adult rabbits, these cells are rather scarce, the fuchsinophile granules are heaped up irregularly, and the nucleus is sometimes wanting. In adults the granules appear to undergo regressive changes; the protoplasm seems to be arranged in irregular granules, but little distinct: also the gland preserves its epithelial aspect in some parts only: usually large numbers of Cerletti's "perivascular corpuscles" are seen. The pineals of the sheep, young and old, ox and calf, and pig contain many neuroglial cells with long interlacing processes terminating among them: many typically glandular elements are also found. After a period of rapid evolution, their pineals undergo a regressive change in the adult.

COSTANTINI[53] (1910) studied the pineal of ox, horse, and Man: he notes that the pineal of the ox and horse is twice as large as Man's, though their brain is much smaller. He finds the organ is very vascular; he describes two sorts of cells, viz., acidophile and basophile; he lays great stress on the granular nature of the pineal cells, and concludes that the mammalian pineal is an organ with an internal secretion.

CUTORE[54] (1910) is stated to have found, in many mammals, in addition to neuroglial elements, cells of epithelial character, and also lymphatic elements. In *Macacus* he found abundant medullated nerve-fibres, which form a plexus: but he failed to find this in other mammals. The pineal of *Cercopithecus* shows an evidently glandular structure.

GALASESCU and URECHIA[55] (1910) describe by the name of "paravascular acidophile" cells which they find round some of the vessels of the pineal: these cells are round or oval, with well-coloured nuclei, situated in the midst of a protoplasm which stains vividly with eosine, van Gieson's fuchsine, &c. The protoplasm, which is clearly delimited, contains sometimes fine granules; and sometimes it is so packed that the nucleus is indistinguishable. These cells resemble those of the parathyroids. The two writers suggest that these cells in the neighbourhood of the vessels may play a part in an internal secretion of the pineal body.

Krabbe[56] (1911) studied 100 human pineals, male and female: the ages of the subjects varied between 14 and 92 years: also some pineals from newly-born children, and some from children up to 7 years of age; but unfortunately he was not able to study any between the ages of 7 and 14 years. He found two types of cells in the parenchyma, viz., (1) special "pineal" cells, and (2) neuroglial cells. The former are much the more numerous: their nucleus is large and usually oval: there is but little chromatine, and that chiefly at the periphery: there is usually a nucleolus. The protoplasm is relatively slight in amount: the position of the nucleus varies. He thinks that granules leave the cell-protoplasm to traverse the intercellular spaces and enter finally the blood, or lymph, or cerebro-spinal fluid. On one point he feels certain, viz., that the nuclear products are not gathered by the paravascular granules, because these cells appear to be commoner in cases in which the parenchyma has been destroyed and consequently cannot be the path of nuclear secretion. Some of the nuclei are hollowed out; he supposes that the nucleus is regenerated after evacuation. In young subjects he sometimes found small groups of cells differing from the "pineal cells" in that the nuclei are very small and very rich in chromatine, the chromatic granules are very fine, and the cells are situated more deeply. These cells resemble those of the newly-born; and Krabbe looks on them as pineal cells which have retained their infantile characters. With regard to the neuroglial cells, he thinks that Dimitrova's interpretation of her own figures is not exact, for "it is not enough to say that a cell is neuroglial merely because it is in contact with neuroglial fibres." He gives reasons (p. 263) for his doubt. He goes on: "One must modify Dimitrova's teaching that the pineal is formed essentially of neuroglial elements, and say that its parenchyma consists of non-neuroglial cells between which there are a smaller number of cells (neuroglial) which give off a very large number of fibres which intersect the other cells." Krabbe describes also other cells, and certain variations of the connective-tissue of the pineal: he says there is no doubt that augmentation of this tissue is a process of involution, such as exists in the whole gland. He failed to find any relationship between the secretory process of the nuclei of the "pineal" cells and the augmentation of this tissue. He found, by the Kulschitzky-Wolters method, medullated nerve-fibres, not, however, in the parenchyma nor connective-tissue; but only at the base of the gland a small nerve-bundle, coming from the posterior commissure, possibly aberrant. He found calcifications, usually in the parenchyma, in a few cases in the septa (small and elongated); pigment (lipochrome) in the connective-tissue, parenchyma, and in the cells whose nucleus is divided; fat, but never much, in the septa sometimes: it plays a less important part than the lipoid substances. He never found muscle-fibres; he often found, but not constantly, the neuroglial plaques described by Marburg[68] in 1909. Small cysts are common: only once were they as large as a pea: most were scarcely larger than a pin's head: they are always of the type described by Marburg as the result of central softening of the neuroglial plaques. Krabbe concludes that the pineal of Man shows signs of involution. To the signs described by previous writers, viz., concretions, proliferation of connective-tissue, and neuroglial plaques with their cysts, he would add a fourth, viz., the presence of cells of disintegration. The various forms of cells he found in the septa have certainly no productive function, they are rather the expression of involution of the pineal. On the other hand, he finds evidences which suggest that the adult human pineal has a function. He has been struck by the integrity which the pineal of Man shows from early adult life to extreme old age. Ordinarily, involution begins towards the age of 7 years: but even at 92 years Krabbe found no greater changes than at the age of 14 years, with the exception of sclerosis of vessels. While it is true that degenerative processes are seen in the young, it is also true that the pineal even of the old shows signs of a function. In only one case did he find total degeneration. If the pineal has a function, it lies in its parenchymal "pineal" cells. Krabbe gives reasons why the evacuation of nuclear granules into the cell-protoplasm is not the expression of a degenerative process, thus: (1) the nucleus regenerates after evacuating its droplets; (2) other organs—*e.g.*, epididymis, pancreas of salamander—have similar processes of evacuation of products of secretion of the nucleus into the protoplasm; (3) these processes occur throughout life without the disappearance of pineal cells. He adds significantly that, if they represent a process of annihilation of the gland, it is surprising that the gland, after seventy years of annihilation, preserves almost the same appearance as that of one from a child of 14 years! He is rather sceptical on the subject of pineal syndromes: he thinks that pineal tumours may possibly have an action (? trophic) on nerve-centres situated near the pineal gland. He tried—in a single rabbit—the effect of an injection of pilocarpine on the pineal, which was subsequently examined histologically; but he was not able to draw any conclusions from his findings.

Jordan[57] (1911) gave an excellent description of the microscopic anatomy of the epiphysis of the Virginian Opossum, both male and female adults. Macroscopically, it is a simple tubular evagination of the roof of the third ventricle; it thus recalls the embryonic form of the epiphysis of lower vertebrates, and appears to represent a condition of primitive or arrested development. Jordan finds two types of epiphysis in the opossum, viz., (1) the short tubular or cup-like type, such as is seen in lower mammals and carnivora especially, and (2) the long tubular type of birds and reptiles. These types are illustrated. The opossum's epiphysis is much less vascular than the pineals of sheep and higher mammals. Delicate bundles of medullated nerve-fibres are discernible throughout the entire inter-commissural portion of the epiphysial region. The epiphysis proper shows a few small tubules or alveoli: in no case could they be traced into the lumen of the epiphysis. Neuroglial fibres are chiefly coarse or fine, but some are of intermediate grades: neuroglial cells are also found. On the question of a possible secretion, Jordan thinks that observations on the opossum's epiphysis indicate that the mammalian pineal is unimportant for body metabolism. He writes: "This is not necessarily an admission that it elaborates no secretion which may even exert specific effects, but only that it is not essential either directly or indirectly for the normal conduct of the vegetative functions, as are the secretions of other of the better understood ductless glands."

In November 1911 Jordan[57] followed up his paper on the opossum by a very suggestive study of the histogenesis of the pineal body of the sheep. He studied six stages in all, from that of a 5 cm. embryo (about the second week) to the 21 cm. stage (about 2½ months, *i.e.*, half way through gestation). He studied also the pineals of the animals at term, of lambs aged about 8 months, of yearling sheep, and of old sheep. The pineal at term is exactly like that at 8 months, except that the latter is larger. At half way through gestation the alveoli and melanic granules are most abundant. At term the sheep's pineal is very vascular. At 8 months of age it attains its maximum size (about 8 × 5 mm.). Jordan writes: "The greatest increase in bulk (approximately five-fold) during the first year indicates that, if the pineal body has a specific function, this is most active in the young; and the suggestion frequently made that the body is a gland which elaborates an internal secretion which has to do with the normal growth or the appearance of maturity (sheep mate at from 6 to 8 months) receives support from anatomical facts." He found increase of size in the pineals of young children, *i.e.*, in an infant of 5 days it was 3 × 2 × 1 mm.; in youth it is largest, about 7 × 5 mm.; in old age considerably smaller. The abundance of melanic granules found half way through gestation "indicates that the secretory activity of the 'gland' may be greatest at this stage of development." Jordan failed to find chromaffin cells, which some authors describe, in the pineal; most workers (according to my own reading) agree with Jordan on this point. He could not find any striped muscle-fibres. "Nor do the trabeculæ here contain smooth muscle-fibres as noted by some investigators for certain forms (*e.g.*, ox; Illing,[59] 1910)." He failed also to find nerve-cells; and pigment-clumps occurred only in old sheep. Contrary to Dimitrova's negative findings, he found brain-sand in the proximal portion of the pineals of yearling sheep, and a large amount in old sheep. After the first year the sheep's pineal becomes slightly smaller (6 × 4½ mm.); this lessening in size is accompanied by a decrease in the parenchymal cells and an increase in the connective-tissue and neuroglial elements. In old sheep there are evidences of several degenerative changes. Jordan has a long description and discussion of the cytoplasmic granules: the nucleus contains only chromatic granules, the cytoplasm only melanic granules. He concludes that there is no cytologic evidence in favour of a secretory function of the sheep's pineal; but he is careful to point out that "its general structure (*i.e.*, lobulation, connective-tissue framework, arrangement of parenchyma into follicles, presence of blind alveoli large perivascular lymph-spaces, great vascularity, and presence of granules in the cytoplasm) indicates a glandular function of the nature of elaborating an internal secretion. The parenchymal cells are all of one type: more or less highly differentiated ependymal cells, giving origin to neuroglia cells and fibres, and inter-neuroglia cells." He interprets the cysts and the melanic cytoplasmic granules as having probably only an ancestral significance. The importance of his paper is very great.

Biondi[58] (1912), whose work I know of merely by a single brief abstract, studied the avian pineal, chiefly (I believe) that of the adult hen, by Golgi's arsenious acid method; the parenchymal cells were studied by another method for the demonstration of mitochondria. He appears to describe granules in the parenchymal cells of the hen's pineal which he is inclined to look on as mitochondrial formations; but he seems to admit that the matter is not yet quite settled. One may recall here the fact that P. Mulon has described (*Compt. Rend. d. l. Soc. d. Biol.*, 1911, i., p. 652) in the cortex of the adrenal of many mammals an internal secretory process in which mitochondria elaborate a complex lecithalbumen which is discharged from the cells into the blood-stream. This is of special interest because there is some evidence in favour of the view that the cortical adrenals are connected with the sex-functions and probably bodily growth also; a relationship with the pineal body is thus suggested, but its exact nature is at present unknown.

I have not attempted to give any detailed account of the important 1909 paper of Marburg,[68] as I know of it only by scattered and fragmentary references by other writers; but some of his findings are noticed in my account of Krabbe's paper[56] (1911), and Münzer[87] seems to rely largely on Marburg's paper in his own general survey of the pineal body.

After this histological section was written, an important paper by Funkquist[60] appeared on the morphogeny and histogenesis of the pineal organ in birds and mammals. He worked by numerous methods: and his technique is fully described. His studies included the hen, duck, diver, canary, and sparrow; the ox, pig, rabbit, rat, hedgehog, and cat. The turkey-cock is also mentioned once. The variations in both classes are considerable. In birds and mammals the epiphysis is developed as a pocket-shaped outgrowth from the roof of the pars parencephalica (v. Kupffer) diencephali, which later is changed into a tubular structure of varying length. In certain birds (diver) this separates often from its connection with the brain. In both classes two types of epiphysis are found, viz., (1) a simple tubular one: its growth is by enlargement of its circumference and thickening of its walls: it is found in sparrow, canary, opossum, and ox; (2) a budding tubular form: in many instances the tubules are detached from the pineal pocket; this type is found in diver, duck, hen, rat, hedgehog, cat. Originally, the embryonic epiphysis has an epithelial character: later its character is transformed into a neuroglial tissue. Two types of cells are described, viz., ependymal cells, and astrocytes. The author never found brain-sand in avian or mammalian embryos, but only in adult mammals: he found plenty in a 3-year-old mare, in older oxen, cows, and sheep. He never found true nerve-cells or fibres, nor muscle-cells. He suggests that what some authors have taken for muscle-cells may really have been a " myoid " development of neuroglial cells.

4. Clinico-Pathological.

Out of about sixty-five recorded cases of tumours of the pineal body metabolic symptoms and signs have been present in about 10 per cent. To these metabolic cases I shall refer, and also to two cases recorded by Pellizzi,[71] and to one of the two cases of sexual precocity recorded by Machell.[72] Among other lesions which occasionally involve the pineal body, either primarily or secondarily, are, according to Seigneur,[6] (1) hypertrophy (Virchow, Meckel, Œsterlen, Lieutaud, Morgagni, Blanquinque, and Marburg; other ancient cases are said to be given by Legros[3]); (2) atrophy (Morgagni, Laignel-Lavastine—an unpublished case); (3) cysts, of which Marburg[68] recognises two varieties: Virchow and older writers also record cases); (4) hæmorrhages (Ziegler, Simon); (5) syphilis (Lord,[48] possibly Pontoppidan); (6) abscess (Birsch-Hirschfeld).

The cases of pineal tumours with metabolic symptoms may be classified as (1) cases occurring in very young male children associated with bodily, sexual, mental, and vocal precocity; (2) cases associated with obesity; (3) mixed cases. But needless repetition would be necessary if the cases were detailed according to such a grouping. I propose, therefore, to give the cases in chronological order.

Gutzeit's Case[61] (1896).

A boy of 7¾ years, strongly built and well developed, showed abundance of pubic hair during the last eight months of his life when intracranial signs were present. Pappenheimer[64] states—without giving any particulars—that other marked signs of precocity were present. [I have not had access to Gutzeit's paper; and all the many abstracts of it, which I know, are very meagre.] Autopsy showed a teratoma of the pineal, which had compressed the corpora quadrigemina.

? HEUBNER'S CASE[62] (1898-99).

I have not had access to the publication in which Heubner records this case. There are great discrepancies between various writers about the case; thus, Bailey and Jelliffe[63] describe it as a separate case from that of Œstreich and Slawyk (see below): whereas Seigneur[6] describes the case as the case of Heubner and of Œstreich and Slawyk. The similarity in the autopsy findings in the (two?) cases suggests that Seigneur is right. Heubner's case is generally described as being in 1898 a 4½-year-old boy: yet he seems to become in 1899 a 4-year-old boy! I find in Œstreich and Slawyk's paper no mention of Heubner's name. But v. Frankl-Hochwart[69] writes of Heubner's case as "published by Œstreich and Slawyk"—"a 4-year-old boy." Marburg[68] (1908) has no mention of Heubner's case, but he refers to the case of O. and S. as a 4½-year-old boy. Raymond and Claude[70] say the boy was 4; they too ignore Heubner's name in connection with the matter.

It is stated by Pappenheimer[64] that in 1898 Heubner reported, before a German Society in Düsseldorff, the case of a boy of 4½ years, who in his last illness showed a marked development of pubic hair and growth of the genitals. From other abstracts I gather that the large size of the penis and testes, and the pubic hair, appeared with the intracranial symptoms. It is said that Heubner showed a photograph of the patient. It is also said that the case was later examined by Œstreich and Slawyk. Autopsy: a cystic psammo-sarcoma of the pineal.

ŒSTREICH AND SLAWYK'S CASE[65] (1899).

A boy of 4 years of age. Birth with forceps: was a long time asphyxiated: laryngismus at 3 months. He developed normally during his first year. When 1 year old, had convulsive attacks. When he was 3 years old, the formerly bright boy showed a strikingly quiet and shy disposition: he sat in the corner most of the time, and cried much. At this time he began to grow quickly and vigorously, and his bodily overgrowth was excessive. His penis developed enormously: this was attributed by the parents to masturbation, but there was no proof of this. When 4 years old, the boy looked 7 or 8, was very bony and muscular, and had plenty of fat: his skin was of natural colour. Height 108 cm. (3 ft. 6½ in.), *i.e.*, about 6¼ in. too tall for his age. Weight 20 kilos, *i.e.*, 4 too much. Mammary glands hypertrophic, contained colostrum, and measured 2 cm. ($\frac{4}{5}$ in.) in height. The flaccid penis measured 9 cm. ($3\frac{9}{16}$ in.) in length. Testes as large as a pigeon's egg. Abundance of dark pubic hair, 1 cm. ($\frac{2}{5}$ in.) long. Extremities of natural length, and no thickening of phalanges. Mentally, he was quiet but not sad, and somewhat precocious ("altklug"). Towards the end of his illness his weight rose to 22·3 kilos, and then slowly sank to 19·5 kilos. Definite intracranial symptoms appeared during the last four weeks of life. [This statement differs from Pappenheimer's account[64] of the so-called

"Heubner's case": according to O. and S., genito-somatic overgrowth began at 3 years, and lasted for twelve months: then appeared signs of intracranial disease: the importance of these points is very great.] Autopsy: a cystic psammo-sarcoma of the pineal. The pituitary, thyroid, adrenals, and pancreas were normal, both macroscopically and microscopically. The thymus showed no visible pathological changes: it was 7 cm. long, 3½ wide, and 1 cm. thick.

C. OGLE'S CASE[66] (1899).

His case 2 was a boy of 6 years, who had been strange in his manner for the last few months, had masturbated, and had slept much. His penis was the size of that of a boy of 16 or 17: pubic hair fairly plentiful: testes "did not seem enlarged." Autopsy: an alveolar sarcoma of the pineal, with hæmorrhages: the pituitary was normal microscopically.

M. NEUMANN'S CASE 2[67] (1901).

A boy of 11 years had acute symptoms like those of tuberculous meningitis only ten days before his death. There was slight development of the external genitals. Autopsy: a cystic sarcoma of the pineal.

MARBURG'S CASE[68] (1908).

A girl of 9 years began to grow fat about one year after the earliest intracranial symptoms appeared. The adiposity was great on the chest and abdomen: the fat was more than 5 cm. thick (2 in.): no other anomalies of growth were present, and there were no genital or sexual changes. Measurements of height and weight are given. Death followed on operation. Autopsy: a mixed glio-sarcoma of pineal. The pituitary and all the other endocrine glands were normal. Marburg concluded that, as he found all these glands normal, and the pineal showed a multiplication of its glandular elements as well as of its neuroglial tissue, the adiposity was to be attributed to a hyperpinealismus. And he enunciated the following three pineal syndromes: (1) hypopinealismus (in early life) gives premature development, genital, sexual, somatic; (2) hyperpinealismus gives adiposity; (3) A-pinealismus, cachexia.

VON FRANKL-HOCHWART'S CASE[69] (1909).

A boy of 5½ years with marked genito-somatic, psychical, and vocal precocity. His father and two paternal uncles had persistent branchial clefts: a sister a hæmangeioma of the labium: a younger brother a nævus on leg. When the patient was 3 years old he began to grow rapidly and excessively, and showed mental precocity. When 5 years old he was heavy and stout, and looked 7 years old: at this time his mental precocity reached a truly astonishing degree; thus, he spent much time in discussing the question of the immortality of the soul, and the life after death: these ideas and subjects were not suggested to him by his relatives or friends. He was sensitive and good-hearted. It was at this time (5 years 1 month) that he showed his first signs of intracranial disease (August 1908). Early in December 1908 he showed great development of the penis, strong erections, marked growth of pubic hair, and moderate growth on tibiæ: his voice was extraordinarily deep, and resembled that of a boy's breaking voice at puberty. He was seen by v. Frankl-Hochwart on 13th January 1909, *i.e.*, nine days before death. He then showed subcutaneous fat, and strong bony development: height 123 cm. (4 ft. ½ in.), *i.e.*, that of a boy of 9 years: penis 7 cm. long (2¾ in.): pubic hair equal to that of a boy of 15: testes the size of a hazel-nut: no axillary hair. The diagnosis was "tumor cerebri destroying the pineal." Autopsy: a pineal teratoma, composed of neuroglial elements, papillary granulations, epidermic globes, and hyaline cartilage. Pituitary microscopically normal.

RAYMOND AND CLAUDE'S CASE [70] (1910).

A boy aged 10 years: birth normal: family history good. At the age of 7 years he was rather large, and his intelligence was very much developed. At age of 8 his stature was above the average, and his size was rather big. He then became fat and weak: the adiposity continued for a year or more. When examined at the age of 10 by the authors, his figure was a little swollen and bloated ("bouffie"), and his colour slightly pale. Height 138 cm. (4 ft. 6½ in.), *i.e.*, that of a boy of 13 or 14. Weight 39 kilos (average is 25 or 26): and the parents affirmed that he had been for six months losing flesh. There was adiposity of abdomen, thighs, and lumbar region: his cheeks were chubby. Mental apathy: but he answers questions well, perhaps slightly better than most boys of his age: memory good: slight depression: but otherwise his psychical state was good. He had pubic hair, equal to that of a boy of 14 or 15: and slight down on cheeks and upper lip. But the penis was very short and small, and the testes very small. The diagnosis of pineal tumour was made. Autopsy: a glioma of the pineal. Pituitary small: its glandular elements, however, were normal in appearance: "still its glandular functions were certainly impeded": the diminution of its size was attributed to mechanical compression. The testes measured 10 × 8 mm.; they showed no evidence of spermatogenesis: their interstitial tissue was over-developed. The testes were microscopically abnormal for his age and for the general degree of good bodily development. The adrenals showed changes:—the cortex contained nodules like hypernephroma, *viz.*, groups of cells forming a rounded nodule, and containing fat; the medullary substance was also very well developed, and contained very many more eosinophile cells than normal. These changes pointed to a general hyperfunction of the adrenals. The pancreas was normal, with well-developed islets of Langerhans. The thyroid body was rather small, but showed no other obvious changes. The authors discuss the question of pineal syndromes, and conclude that adiposity and genital troubles are really due to a pluriglandular syndrome.

There are several recorded cases of pineal tumours, verified by autopsy, in which some degree of adiposity has been noted: but I think no good purpose would be served by further reference to them. In my opinion, it is not yet proved that adiposity is ever of purely pineal origin. Incidentally, this point will be referred to in the section on experimental procedures.

There are, however, still three cases which deserve mention here, though it is true that the existence of any pineal lesion, gross or functional, in them is unproved.

PELLIZZI'S PRECOCIOUS GENITO-SOMATIC PINEAL SYNDROME (1910).

Under this title Pellizzi[71] has described two cases in young boys. [I greatly regret that I have not had access to his paper; and in the only abstract of it, known to me, no statement is made whether intracranial disease was found: for aught I know to the contrary, both children may be still alive.]

Pellizzi's Case 1.—In the abstract there is no mention of the boy's general health: this may mean that it was quite good. Marked bodily overgrowth began at the age of 7 months: at age of 2 years penile erections and seminal emissions: *the semen was proved to contain spermatozoa*: no sexual libido accompanied the emissions: no onanism. The genitals resembled those of a man: the pubes was moderately covered with hair: there was a suggestion of a moustache. Psychical condition good, corresponded with that of an older child. Radiography showed a condition as of a youth of 16 or 17: but the dentition showed the true age. The abstract contains no further particulars.

Pellizzi's Case 2.—The abstract says that the history was less reliable than in case 1. In this boy bodily overgrowth began at the age of 2 years. He was hydrocephalic, and his mental capacity was very limited. The genital development corresponded approximately to that of case 1. (This last sentence is not exactly satisfying, and no further particulars of the case are given in the abstract.) The presence of hydrocephalus of course makes us think here of a tumour of, or involving, the pineal. But in case 1 there is an alternative possibility which will be referred to in the section of this paper on the "General Discussion."

MACHELL'S CASE 2[72] (BOY) OF SEXUAL PRECOCITY (1911).

In January 1912 I abstracted this case in *The Review of Neurology and Psychiatry*, and suggested that a pineal lesion was probably present: this I will discuss in my general discussion.

A boy showed pubic hair at the age of 5 months: erections one year later: emissions when 2½ years old. His father, aged 33, weighed 12 lbs. at birth, and developed early: he is now, however, only 5 ft. high, and weighs in clothes only 103 lbs.: he is the small one of the family: he has three brothers of normal size, the youngest of whom developed early: he has also two sisters, who menstruated at the usual age and are of average height and weight. A photograph of the patient shows pubic hair and great penile development, and a very finely built sturdy frame of good proportions. His weight at 4 months of age was about 7½ lbs. too great: at 8 months 12 lbs. too great: at 12 months 13 lbs. too much: at 3 years 20 lbs. too much. At the age of 44 months his height was 3 ft. 9½ in. (8½ in. too much). At age of 4 years his head was 2·3 in. too large in circumference: his chest nearly 5 in. too large in girth: his penis measured 2⅞ in. when lax: it was very large when erect: emissions, both spontaneous and on manipulation. Mental precocity very marked: disdains toys of tiny tots: habits those of much older boys: manner independent: he is perfectly self-possessed with strangers even, answering questions in a loud, bass, stentorian voice. Machell makes no mention of the boy's general health: it seems probable, then, that it was good. The boy was born in February 1906: he was therefore less than 6 years old when Machell's paper was published (November 1911).

Directly I read Machell's paper I was struck by the extraordinarily close resemblance of his case 2 (boy) to v. Frankl-Hochwart's case,[69] so far as the bodily, genital, sexual, mental, and vocal development was concerned. In my general discussion I shall refer to Machell's case again, and show that, as in Pellizzi's case 1, there is one, and only one, other lesion besides a pineal lesion that, in the present state of our knowledge, is to be thought of.

By the kindness of the Editor of this *Review* I am able to draw attention to an important case which came to my notice after my MS. was sent in. I refer to the case recorded by E. Cecil Williams (*Proc. Roy. Soc. of Med.*, section of study of Disease in Childhood, Vol. 6, Nov. 1912, p. 24). It was one of precocious development in a boy aged 6 years.

About November 1911 the boy began to develop quickly: he was admitted to hospital in May 1912. At that time his weight was 4 st. 2 lbs.; height 4 ft. 2 in.; he has a slight moustache; his voice is deep, like an adult's; the muscles of his arms and his trunk are well developed; he can lift heavy weights; he is slow of intellect and movement, and cannot run as other boys of his age do; he is inclined to knock-knee, and his tibiæ are inclined to be curved. Pubic hair is abundant, but there is none in the axillæ; his external genitals are fully developed. All these changes are shown in a photograph. No tumour can be felt in the abdomen, and there is no bronzing of the skin. His blood-pressure is high (110 mm. Hg.). His urine is normal. The head-circumference is 21½ in. The boy put on 11 lbs. in weight during his five weeks' stay in hospital. Fresh measurements were taken in October 1912; the particulars given show marked increase of weight, height, and of neck and chest measurements. The author discusses the possibility of a tumour of the cortex of the adrenal or of the pineal body. A skiagram of the skull was thought to indicate a slight enlargement of the sella turcica and pituitary fossa. The president of the section thought that there was also an early development of the sphenoidal sinuses: unfortunately, the skiagram is not given. It is stated that in October 1912 the boy's general health is excellent; but there is no mention of the reason why he was admitted to hospital in May 1912; possibly the state of his lower extremities was the reason. It is noted that the ocular fundi were normal.

The special interest of this case arises from the suggestion that a lesion of the pituitary body, or of its neighbourhood, may be present. If subsequent study should prove this to be the case, then it will be the first case on record in which a pituitary lesion has led, either directly or indirectly, to the macro-genito-somatic precocious syndrome in a boy of the early age of six years. Further, we should then have to modify our conceptions of this syndrome in boys under the age of seven years, and to say that in such cases three possible diagnoses are open, viz., (1) a lesion of the pineal body, (2) of the adrenal cortex, (3) of the pituitary body. Everyone will notice the striking difference between the mental precocity and independent manner of Machell's case and the slowness of intellect of Williams' case. It seems probable that the inability to run in Williams' case is due entirely to the state of the boy's lower extremities.

5. EXPERIMENTAL.

(1) *Extract-Injection Method.*

[I shall make use here of the term "pinealine"—which I have coined—to denote an extract made from the pineal body.]

W. H. HOWELL[73] (1898), in the course of a study of the physiological effects of injection of extracts of the sheep's hypophysis and infundibular body on dogs, found that glycerine extracts of pineal body (probably of sheep, but the source of the pinealine is not stated) gave inconstant results on blood-pressure, viz., sometimes a very slight fall, or none, at others a marked fall. Unfortunately he did not pursue his pineal experimentation any further.

E. VON CYON[74] (1903) found that intravenous injection into rabbits of pinealine of the ox and the sheep had no effect on blood-pressure; small doses gave a feeble and frequent pulse: large doses a bigeminal or trigeminal pulse, which disappeared after section of the vagi. He attributed the effects to the presence of salts in the epiphysis, especially phosphate of calcium.

Dixon and Halliburton[75] (1909) found that sheep's pinealine—prepared in four distinct ways—when injected intravenously into cats, fully anæsthetised with urethane, gave a slight fall of blood-pressure, which was transient: chemical examination showed that it was not choline which caused this fall. They concluded that other physiological methods must be employed for the purpose of deciding whether the mammalian pineal has any function.

In 1910 these two authors,[75] experimenting on dogs, anæsthetised with urethane and morphine, found that, while extracts made from the choroid plexuses of ox, sheep, and man, injected into the sub-cerebellar cisterna, or the lumbar region, cause a flow of cerebro-spinal fluid, pinealine has no such effect.

Ott and Scott[76] (1910-1911) reported at a meeting of the Society of Experimental Biology and Medicine, New York, in December 1910 (their full paper appeared in October 1911) that intravenous injection of boiled pinealine (source not stated) had a rapid galactagogue effect on lactating goats. Five grains of pinealine were needed for this effect: one-grain doses had no such effect. No etherisation was used, and the method of Rohrig was applied in these experiments. They got galactagogue effects also with thymus extract (1 gr.), corpus luteum extract (10 grs.), and infundibulin. The galactagogue effect of pinealine was less than that of infundibulin.

In April 1912 these two authors[76] added several new points on the effects of intravenous injection of pinealine and of corpus luteum extracts. The effects of both on the circulation were nearly identical, viz., initial depression of blood-pressure, followed by a rise above normal for a short time: the pulse-rate was not appreciably altered. While corpus luteum had no effect on the kidneys, pinealine caused diuresis and increase of kidney volume due to vaso-dilatation. Application of pinealine to a uterine strip of the rabbit *in situ* caused increased contraction of the pregnant uterus but not of the non-pregnant, whereas corpus luteum extract caused both, but only slight in the case of the non-pregnant uterus. On an excised strip of rabbit's intestine, pinealine gave slight increase of contractions, while corpus luteum gave greatly increased contractions. Finally, in rabbits whose superior cervical sympathetic ganglion had been excised, local application of pinealine gave slight pupillo-dilatation.

In May 1912[76] Ott and Scott reported that a preliminary intravenous injection of gr. $\frac{1}{50}$ of atropine lessens the galactagogue effects of a subsequent injection of pinealine, corpus luteum extract, and infundibulin. They add that pinealine dilates the renal vessels; and they suggest that, as pinealine, corpus luteum extract, thymus extract, and infundibulin are vaso-dilators in the male genitalia, it is probable that they are also vaso-dilators in the mammary gland.

JORDAN AND EYSTER[77] (1911).

> [I have placed their names before those of Schäfer and K. Mackenzie, for though their full paper did not appear till December 1911 (*i.e.*, after that of S. and M.), yet it appeared in abstract before that of S. and M., *i.e.*, in the *Proc. Amer. Physiol. Soc.* for February 1911 (*Amer Journ. of Physiol.*).]

These two investigators performed intravenous injections of sheep's pinealine—but in a more concentrated form than that used by Dixon and Halliburton[75]—into dogs, cats, a rabbit, and a sheep. They confirm the findings of Dixon and Halliburton that the effect on the cat's blood-pressure is small. They found that, with a fall of blood-pressure, there was a vaso-dilatation in the intestines, a slight improvement in the beat of the isolated cat's heart, and a transitory diuresis (associated with glycosuria in about 80 per cent. of the cases). They found also slight effects on respiration: in a sheep there was gradual increase in depth, lasting for some time after the injection. They note that these pinealine effects are relatively slight when compared with those of other glands known to furnish internal secretions.

SCHÄFER and K. MACKENZIE[78] (July 1911) failed to confirm the earliest findings of Ott and Scott[76] (1910) on pinealine and on thymus extract, but confirmed them on infundibulin and on corpus luteum extract. The source of their pinealine is not stated. Their work was performed on lactating animals—chiefly cats, but also a few dogs.

K. MACKENZIE[79] (December 1911), in a renewed study of the subject, found that intravenous injection of boiled pinealine of sheep gave a small, but distinct, stimulating effect on mammary secretion in cats in varying stages of lactation. He thought that the pinealine effect "might be due to the presence of a small quantity of pituitary extract absorbed from the surrounding cerebrospinal fluid, but he failed to obtain any effect from the cerebrospinal fluid itself, also from extracts of brain substance." He suggests that, if it were sufficiently inspissated, the cerebro-spinal fluid might possibly show the presence of the pituitary galactagogue; but he had not had an opportunity of trying this experiment at the time of sending in his MS.

(2) *Electrical Stimulation Method.*

E. VON CYON[74] (1903) appears to be the only observer who has applied the method of electrical stimulation of the exposed pineal body. He succeeded in doing this in the rabbit. He obtained a lessening in size of the pineal with a slight change in its position, but no alteration of its colour: he therefore rejects a vaso-constriction as the cause of the diminution of size. It is very unlikely that either striped or unstriped muscle-fibres are responsible for this diminution of volume, for no one has ever found either kind in the rabbit's pineal. Von Cyon admits that the pineal contraction causes mechanically a flow and afflux of cerebro-spinal fluid. The suggestion has been made that the lessening of size may be due to an inhibition of pineal secretion: but we must remember that at present we lack conclusive proof that the pineal really has a secretion to be inhibited, though such a hypothesis will probably prove to be correct.

(3) *Destruction of the Pineal by Cautery.*

SARTESCHI[52] (1910), who operated on eleven rabbits, is said to have adopted this method in some instances; but his results were negative.

EXNER AND BOESE[80] (1910) applied this method to young rabbits; only six out of ninety-five animals lived to the period of sexual maturity. Their results were negative.

We are now able to understand why the method has proved a failure; for recently Foà[81] has shown that it is not possible to destroy completely the rabbit's pineal by the cautery. He refers to Staderini's[82] study of the topography of the rabbit's pineal body:

he shows that the method adopted by Exner and Boese could, in most instances, destroy only that part of the rabbit's pineal which is situated between the vermis cerebelli and the cerebral hemispheres: Foà finds that the rabbit's pineal is 15 to 16 mm. in length, by 5 to 6 mm. breadth in its distal portion: he found that in the rabbit the danger of wounding venous sinuses and of damaging the vermis cerebelli or the occipital lobes is very great: in short, it is not possible to even extirpate the rabbit's pineal completely.

It follows from this that the negative findings from the application of the cautery method are due to the fact that the destruction of the pineal was incomplete.

(4) *Extirpation of Pineal Body.*

Sarteschi[52] (1910) applied this method in some of his eleven rabbits: only two survived, both being females: in one the extirpation was said to be complete, but the animal died, without discoverable cause, four months after the operation; both these female rabbits became very emaciated and had a retardation of development; though both animals were kept with males, they did not breed. [It seems very doubtful, from the abstracts of Sarteschi's paper known to me, whether this was connected with the pineal body at all: possibly the post-operative emaciation was responsible: in any case, in only one of the two animals was the extirpation claimed as a complete one.]

Exner and Boese[80] (1910) attempted this method in some of their ninety-five young rabbits; of these, twenty-two were kept for a long time: but only six till puberty, three being males. No difference in weight, nor in reproductive faculty was noted. But, as I shall show presently when I come to Foà's researches, it is doubtful whether the extirpation was complete, or is indeed possible in the rabbit.

Biedl[83] (1910) is reported to have performed some extirpation experiments, with negative results. But Foà[81] says that Biedl's account is very short: I have failed to obtain Biedl's important monograph.

Foà[81] (1912) has given us far the most valuable experimental study of the pineal body. But at the outset of his inquiry, he came to the astonishing conclusion that the pinealine injection-method had been worked out, and was not worthy of re-study.

[I pointed out in December 1910[88] that not only is this untrue, but the subject had not even begun to be studied properly, because no one had tested the effects of pinealine taken from very young or newly-born animals. Even now, at the end of 1912, my statement still applies: but I have reason to believe that before long we shall have some experimental work published—on the lines of the suggestions made by me in 1910—by two physiologists, with whom I have been in private correspondence on these and other points concerning the pineal body.]

Foà began his work by a preliminary exact study of the topography of the rabbit's pineal body: he performed a preliminary series of extirpation experiments: he found that it is extremely difficult to destroy the whole of the head of the pineal body of the rabbit without injury to the vermis and the occipital lobes: hæmorrhage is also very great. He found that young rabbits, of 1 to 2 months, died within three days of operation. He therefore examined Gallus: he found that the topography of its pineal resembles that of the rabbit: but he was able to prove that complete extirpation was possible in chickens. He extirpated completely the pineal in sixty-three chickens aged from 3 to 5 weeks: fifteen survived, three being males: at this early age he found it impossible to decide the sex—hence the small number of cockerels surviving. During the two or three months following the operation the animals remained rather smaller than the controls and were torpid and listless; after three months they began to develop vigorously, and their bodily development overtook that of the controls, and remained within normal limits. After eight to eleven months, the combs and the testes of the cockerels showed great hypertrophy; the figures are very striking. One cockerel crowed thirty-six days before the control, mated forty-seven days sooner, showed 35 gr. greater body-weight, his testis was 9 gr. heavier, and his comb 38 gr. heavier, at the age of 8 to 11 months the pinealectomised cockerels showed the same degree of body-development and generative capacity as the controls. In some of the control animals Foà had performed a sham operation which consisted in an exact copy of the full operation with the exception that the pineal body was left *in situ* uninjured. When pinealectomised pullets, which had begun to lay, were isolated with pinealectomised cockerels, their eggs proved fertile on artificial incubation. Autopsy showed no appreciable macroscopic changes when compared with the controls: the examination included brain, pituitary, thymus, thyroid, adrenals, heart, lungs, kidneys, all the abdominal viscera, bones, and panniculus adiposus. Foà reserves a report of the histological findings for a subsequent paper: he promises also a comparative study of the pineal body at various ages. [There is one omission in his excellent paper that disappoints me: he gives no particulars as to the size, or generative capacity, of the progeny of (1) mated pinealectomised cockerels and pullets; (2) pinealectomised cockerels mated with normal pullets; (3) pinealectomised pullets with normal cockerels. The importance of these needed experiments will be clear when my own interpretation of Machell's case of sexual precocity in a boy is referred to in my general discussion.]

Foà's list of formal conclusions is as follows :—

(1) Complete removal of the pineal of chickens, aged 20-30 days, is possible.

(2) (Refers to the early post-operative torpor, listlessness, and retardation of growth already detailed.)

(3) In pinealectomised cockerels there is a premature development of the primary and secondary sexual characters (sexual instinct, crowing, comb).

(4) At 8-11 months the operated males showed hypertrophy of comb and testes.

(5) No macroscopic changes are found in the endocrine glands.

(6) Pullets, pinealectomised during the first month of life, show at the end of 8 to 12 months no differences of development, generative capacity, appearance, or size of organs, from those of non-operated pullets.

Thus he alters Marburg's scheme in one important particular, viz., he points out that a-pinealismus (in cockerels) leads to the conditions—or some of them—described by Marburg as due to hypopinealismus. At present we know nothing of hypopinealismus from an experimental point of view. And it is quite possible, I think, that we never shall.

(5) *Effects of Castration on the Pineal Body.*

Sarteschi[52] (1910) failed to find any changes in the pineal body of animals castrated in early life: from the abstracts of his paper I gather that this applies to rabbits; but, as he studied histologically so many varieties of mammals, he may have applied the castration method in others besides rabbits.

Biach and Hulles[84] (1912) castrated fifteen kittens, aged 3 to 4 weeks: half of each litter were kept as controls: nine lived, viz., seven males and two females; all were kept for seven or eight months. Their pineals were hardened; thin paraffin sections cut, and stained with hæmolæne-eosin. Constant atrophy of the pineal body was found in both sexes: the atrophy is described as involving not only the whole gland but also its individual cells. In one cat, aged 3 months, castration was performed: at this age the cells of the cat's testes are functionally active: exactly the same pineal changes were found as in the castrated kittens. The parenchymal cells of the pineal body were scattered, instead of being compact; and the intercellular spaces were larger than normal. The authors conclude that, while their own observations show that Marburg's hypothesis of the functions of the pineal goes perhaps too far, yet they bear out his assertion of the contrast between the pineal and the pituitary, while they also show—for the first time—that, whereas it is well known that castration causes pituitary hypertrophy, it causes atrophy of the pineal.

(6) *Needed Experimental Procedures.*

Two years ago I drew attention[88] to at least three methods of pineal experimentation that had been neglected by all those investigators with whose writings I was then acquainted. And even now, towards the end of 1912, it is as true as it was in 1910, that (1) pinealine from young animals, (2) pineal feeding, (3) pineal grafting, have not yet been tested. Fortunately, however, this deficiency in our present knowledge of pineal physiology will soon probably be removed by two physiologists with whom I have been corresponding privately on certain aspects of pineal physiology. The best way now to deal with the subject will, I think, be to deal first with pineal feeding, grafting, and the pinealine method, and then to take seriatim the four other experimental methods which I have detailed in the subsection 5 of this section of my paper.

Pineal feeding might be tried (1) on normal animals, young and old; (2) on pinealectomised animals, young and old; (3) on completely hypophysectomised puppies; (4) on castrated animals, &c., &c. Pineal grafting might be tried in the same conditions. In addition both feeding and grafting might be tried on young and adult animals whose thyroid, adrenals, &c., had been previously extirpated.

1. *The Pinealine-Injection Method.*

(*A.*) *Pinealine from Very Young Animals.*—It is to be hoped that, in addition to mammalian and avian pinealine, we shall have tests of pinealine from lower vertebrates; especially snakes, amphibia, and fishes.

(1) Can we thus set up an experimental hyperpinealismus? In all cases a careful histological examination should be made of all the endocrine glands, the bones, subcutaneous fat, and mammary glands (of both sexes); and I think we ought to include also sympathetic ganglia, the so-called paraganglia, the carotid bodies, &c., &c.; in short, our histological examination ought to comprise all the organs of what some writers call "the endocrino-sympathetic system."

(2) Has young pinealine any effects on adult animals?

(3) Does it prolong the duration of life in completely hypophysectomised puppies?

(4) Does it modify the known effects of thyroidectomy, adrenalectomy, &c., in young or adult animals?

(5) Have thyroidectomy, thymectomy, adrenalectomy, or castration (both sexes) any modifying effects on the physiological activity of the pinealine of young animals?

(6) Do extracts prepared from the pituitary and other glands of pinealectomised chickens give their usual injection effects?

(B.) Pinealine from Adult Animals.—Undoubtedly we shall have both a reinvestigation of some of the experimental findings of Ott and Scott, and of K. Mackenzie, and a further and more extended new investigation. There is one striking omission on the part of all workers from the time of W. H. Howell (1898) up to Ott and Scott (1912), viz., no histological examination has followed their experimental studies. In any case I fail to see how anyone, who is familiar with the most recent work of Ott and Scott, can maintain that the adult-pinealine method has been anything like worked out yet: we may yet learn a good deal from it of exact pineal physiology. I may add that it is conceivable that we may one day have a pineal medication; it seems to be about the only form of organo-therapy that has not been tried; but let us pray that it may follow, and not precede, a careful experimental study.

2. *The Electrical Stimulation Method.*

Let us first have a reinvestigation of von Cyon's solitary study of stimulation of the exposed pineal body: but let us have, in addition, an attempt to test the physiological effects of pinealine obtained from a young animal immediately after such direct pineal stimulation. It seems at least possible that some modification of the activity of the pineal might be set up by this direct stimulation of the gland.

Another very important application of the electrical method—not yet tried—is the following: At present we do not know whether the sympathetic nerve-fibres, which Cajal[46] has found in the pineal body, are secretory in function, or vasomotor, or both secretory and vasomotor. We have at present no exact knowledge of the origin of these sympathetic fibres, of their course, nor as to how they reach the pineal blood vessels and the external side of the glandular cells of the pineal body. But it seems probable that (1) they rise in cells of the inferior cervical sympathetic ganglion, (2) pass *via* the vertebral plexus along the basilar artery, and (3) thence along the posterior cerebral and superior quadrigeminate arteries to the pineal arteries. If this be correct, we might expect to obtain some modification of pineal secretion by (1) stimulation of the inferior cervical ganglion or the vertebral plexus, or (2) extirpation of that ganglion. In addition, drugs might be applied in combination with these methods. One would suggest too that, after such stimulation or extirpation, pinealine should be prepared from the gland and its effects tested by injection. I think the extirpation would, in this case, probably have to be bilateral, whereas unilateral stimulation would suffice. But one can hardly doubt that physiologists will, by adopting such methods, add substantially to our knowledge of pineal physiology. We know now that secretory glands are of two types, viz., (1) those which receive true secretory nerve-fibres, *e.g.*, the adrenals *via* the splanchnics, and (2) the mammary gland, whose secretory function has been proved to be capable of acting quite apart from connection with the nervous system. At present we do not know to which category the pineal body belongs. In concluding these remarks I may say that there should be no difficulty in tracing degenerated nerve-fibres into the pineal body, after extirpation of the inferior cervical ganglion, *i.e.*, if its sympathetic fibres have the origin and course which I have here suggested.

3. *The Cautery Method.*

This is a bad method; when it does not fail, it is likely to do too much. Even if definite effects were obtained by its use, we should be forced to discount their value, because it may be correct that pineal syndromes may be due, in part at any rate, to damage done to hypothetical centres, or tracts, situated near the pineal body.

4. *Pineal Extirpation.*

This method may well have a great future; the first thing is, of course, to find out in what animals complete pinealectomy can be performed, as in Foà's chickens, without damage to neighbouring structures and without danger to life. I may just repeat the hope, which I have expressed already, that Foà's researches may be extended in the following directions: What is the size, weight, appearance, sexual activity, and generative capacity of the progeny of (1) pinealectomised cockerels mated with normal pullets, (2) pinealectomised pullets with normal cockerels, (3) pinealectomised cockerels with pinealectomised pullets? Of course a searching histological examination would be made of the endocrino-sympathetic system of the resulting progeny in each category.

5. *Effect of Castration on the Pineal.*

The experiments of Biach and Hulles[84] should be repeated, and should be performed in other animals besides cats. And it is to be hoped that we shall be given a more elaborate histological examination of the pineal body of castrated animals than that given by them.

Further, it is of vital importance that we should learn what is the exact histological condition of the pineals of very old animals which had been castrated during the first few weeks of life. [My reason for insisting on this point will be given in my general discussion.] Finally, we want to know what effects, if any, has castration of very old animals on their pineal body.

In concluding this section, I should like to express the hope that both the analytical and the physiological chemist will teach us something of value on the obscure question of pineal chemistry: one cannot doubt that this method of inquiry has a future in front of it.

6. General Discussion.

We come now to the greatest difficulty of all—what use shall we make of the vast mass of facts which have been accumulated, as the results of the labours of numerous investigators in several fields of inquiry, during the modern era, which may conveniently be said to begin with the studies of Faivre[2] in 1854? First of all, a broad survey of the pineal body from all aspects leads, in my opinion, to one fundamental conclusion, viz., that it is probably functional in all those vertebrates which possess one. The pineal body is not, as so many even good authorities have assumed, a rudimentary, functionless, degenerated, or degenerating and disappearing organ. It is something entirely different, viz., a metamorphosed—perhaps also a metamorphosing—organ. If the pineal were really a degenerating and disappearing organ, Nature has been slow indeed in getting rid of it: she has had ever since the far-distant palæozoic era. Let anyone just think of the fact that modern snakes, which are practically identical with those of the mesozoic era, have an unusually vascular pineal organ. Will he seriously ask us to believe that Nature would send a lot of blood to an organ that has no need for it, and thus keep a certain amount of blood from other organs and tissues which do need it? Now it does not in the least follow that, even if the pineal body be functional in all those vertebrates that possess one, its functions are of necessity identical in all vertebrate classes. We must here remember that we are to-day merely at the threshold of our inquiry into comparative pineal physiology. The alleged absence of a pineal organ in certain lower vertebrates is worthy of a passing notice here: its absence in *Myxinoids* is not in the least surprising; for this group of the *Cyclostomes* is known to be—in the main—a very degenerate one. The absence of a pineal organ in *Crocodilia* is certainly strange, but I suspect that they will yet be found to possess one. For palæontologists tell us that existing *Crocodilia* are practically identical as to size, osteology, &c., with those of the mesozoic era; crocodiles, like reptiles, have lived a nice, easy, lazy life through the ages: it seems unlikely to me that crocodiles should lack a pineal organ while snakes have a highly vascular one. One would also expect to find a pineal organ in *Torpedo*; a reinvestigation is desirable. We see that when an animal type is going to degenerate—as, for example, the *Myxinoids*—it loses its pineal organ entirely: it does not keep one, as do its cousins the *Petromyzonts*, and almost all higher vertebrates: still less does it keep a vascular one. It seems to me that the study of *Myxinoids* tends to show the absurdity of the non-functional hypothesis of the pineal organ of vertebrates. The variations of the vertebrate pineal body are so great that it seems probable that its importance varies in various vertebrate classes, and even sometimes in closely related members. When we come to comparative histological studies, the functional activity of the pineal body is strongly suggested by the work of many investigators, specially Faivre[2] (1854), Leydig[7] (1866), Bizzozero[30] (1871), Hagemann[32] (1871-72), Cajal[46] (1895), Galeotti[47] (1896-97), Dimitrova[50] (1901), Sarteschi[52] (1910), Krabbe[56] (1911), and Jordan[57] (1911).

When we study the clinico-pathological aspects of the pineal body, we see some evidence that it has, in early childhood, probably some relationship with body-growth and sex-characters. But it seems to be difficult to establish very definite conclusions as to pineal physiology from these cases, because not only do pineal lesions fail in 90 per cent. of the recorded cases to give any metabolic symptoms, but, of the 10 per cent. which do give such symptoms, some give mixed symptoms and signs, as in Raymond and Claude's case;[70] whereas others give bodily overgrowth with premature sexual and genital development; and yet others give the latter without much of the former. We can no longer entirely subscribe to Marburg's[68] three syndromes, for Foà's[81] experiments on chickens teach us that a-pinealismus leads to testicular hypertrophy (at a certain age), with over-development of secondary sexual characters, but no marked bodily overgrowth, at least nothing approaching giantism. It is, of course, true that Foà's conclusions on these matters are based on his findings in so small a number as three completely pinealectomised cockerels. It seems at least possible that the cachexia, which Marburg attributes to a-pinealismus, may be not really of pineal origin: but here again we must remember that Foà found in his cockerels an early period of torpor, poor appetite, and listlessness, which passed away, however, with the beginning of vigorous growth. As to Marburg's syndrome due to hyperpinealismus, at present we know nothing whatever of such a state, so far as experiment is concerned, the reason being that no experimentalist has yet adopted my suggestions,[88] made in 1910, as to the application of pineal feeding and grafting and injection of pinealine from very young animals. But the obesity that has been found in some cases of pineal tumours may not, after all, be of pineal origin; for even absence of any recognisable histological changes in the pituitary or other glands in such cases does not exclude the possibility of a dyspituitarismus due to subtle metabolic or chemical changes of which at present we have no knowledge. Then, again, adiposity occurs in so many other conditions, and its modes of production are still so obscure that we must conclude, I think, that it is uncertain whether hyperpinealismus in man ever causes adiposity *per se.* We must wait for the verdict of properly applied experimentation.

As to the embryonic hypothesis of the production of pineal syndromes in some cases of pineal tumours, which was suggested by Askanazy, cited by Pappenheimer,[64] I think we must now dismiss it: the experiments of Biach and Hulles,[84] and those of Foà,[81] seem to point clearly to the existence of a pineal function, in young mammals and birds respectively, which is related to the development of the testes: the experiments of Biach and Hulles include also the ovaries. In connection with the embryonic hypothesis, I may quote here a passage from the monograph of Poppi[85] (1911)—to which I have failed to gain access. Poppi is said to hold that an embryonic lesion of the hypophysis cerebri can, by causing lesions of either the pineal body or the thyroid, alter the thymus which, in its turn, causes generalised lymphatic lesions and especially hypertrophy of the pharyngeal tonsil, which causes a lesion of the pharyngeal hypophysis. But is it a fact that an embryonic lesion of the hypophysis cerebri can cause a pineal lesion?

So far as recent experiments go, we must, I think, provisionally conclude that one of the functions of the mammalian and avian pineal body is to exercise an inhibitory influence on the development of the testes in early life (prepuberal), and, through them probably, on the appearance of the secondary sexual characters. Its relation to the ovaries needs further experimental study in several directions which I need not specify here.

It might be claimed that the embryonic hypothesis may after all be correct: but I think the utmost we can now admit in its favour is that, if embryonic lesions do sometimes lead to definite pineal syndromes, they probably do so by virtue of their stimulating or inhibitory effects on the specific functions of the pineal body.

There is one matter on which most authors seem to lay insufficient stress: we are all so apt in these days to talk of states of excess or defect of secretory processes in endocrine glands that we are in danger of forgetting that possibly perversion of secretion, which may quite well be due to subtle chemical changes which give no recognisable histological alteration, may really be sometimes more important than mere excess or deficiency. Again, it is often forgotten that states of excess and deficiency not uncommonly occur simultaneously in a gland which is the subject of tumour-formation, or pressure. It seems then unsafe to conclude at present that a hyperpinealismus may of itself cause adiposity; for aught we know to the contrary, a dyspinealismus may possibly do so sometimes, and may at other times cause a hypopinealismus or an a-pinealismus, and at still others a mixture of excess and deficiency. If we turn for a moment to acromegaly, we seem to get some confirmation on these points: though the balance of opinion is now that that disease is due to hyperplasia of the glandular lobe of the pituitary, and that Marie's original teaching that it is due to hypopituitarism, is in the main erroneous, yet we know that pituitary medication, which is usually harmful in the disease, has sometimes done some good. We can hardly doubt, I think, that cases of acromegaly vary (as do all diseased states): hyperpituitarism preponderates usually, but it is sometimes accompanied by some degree of hypopituitarism: Marie was therefore not wholly in error. So far as the pineal body is concerned, I think the solution of these matters rests mainly in the hands of the experimentalist and the chemical physiologist.

A reference to Machell's[72] case 2 (boy) seems to be needed here. When I abstracted his paper in January 1912 I drew "special attention to the heavy weight of the patient's father at birth, his early development, and ultimate small size when grown up." I suggested that "this may mean that the patient's father showed a condition of non-fatal hypopinealismus in early life, to which was added during adolescence a condition of hypopituitarismus." I have already indicated the experimental methods—or some of them—by which the accuracy or the error of this suggestion may be tested. It seems to me that we must beware of assuming that every case of hypopituitarismus must of necessity conform in all respects with the full adiposo-genital syndrome of Fröhlich; whereas it is rare, states of incomplete hypopituitarismus are common—unless we are greatly mistaken. What is going to happen to Machell's boy, or to Pellizzi's case 1? [I assume that Pellizzi's case 1 had no ill-health, and is presumably still alive.] Will Machell's boy get intracranial signs and die? If he has really an intracranial tumour, it is very slow in giving any purely intracranial signs. Will this boy, who is now so big, grow up small eventually? Are there sometimes cases of non-fatal pineal lesions—not due to gross disease—which can give effects such as this boy shows? Clearly, all such cases should always, if possible, be followed up to adult life, if they reach it. There seems to be only one known condition, besides pineal tumours, which can for a long time give genital and sexual overgrowth somewhat similar to that shown by Machell's boy, or Pellizzi's boy (case 1), viz., tumours of the adrenal cortex. But, whereas all those cases of pineal tumours, which were associated with genito-somatic precocity, have occurred in boys, cortical adrenal tumours are excessively rare in boys, and never—so far as we know—give rise in boys to genital precocity. It is unlikely, therefore, that Machell's case and Pellizzi's case 1 are examples of cortical adrenal tumours. Of course, if they are, we have an easy explanation of the absence in them of intracranial signs and symptoms. [An immensely large and valuable body of facts will be found in Glynn's excellent paper[86] on adrenal tumours, &c., 1912.]

Many authors have cited the presence in the pineal body of such a large amount of neuroglial tissue as a proof of its functional unimportance. Now I am one of those who hold that everywhere neuroglial cells and fibres have some function, or functions quite apart from their mere mechanical one. Even if the pineal were composed of nothing but neuroglial tissue, we should not be justified in stating that it is functionless. Let the adherents of the "purely supporting nature" hypothesis of neuroglia answer the following questions, if they can: If the pineal body be a rudimentary, useless, disappearing organ, of what possible use to it can a supporting tissue be? What would the supporting tissue support but itself? And how would the presence of a self-supporting tissue that had no other functions benefit any animal organism? No, not only is neuroglia not solely a supporting tissue, but I believe there is no tissue in the animal body that has only that function: every tissue has probably more than one function.

The crucial test whether a gland furnishes an internal secretion consists in recovering from its efferent vein, or veins, a substance which, on injection, gives specific effects. Now, in the case of the pineal body, this test may prove to be difficult of performance: so far as I know, it has not yet been tried. The pineal veins, which enter the veins of Galen of both sides, are small, and might prove difficult of puncture; still, I hope an attempt will be made. It is probable that arterial changes seldom cause pineal syndromes; the human pineal is supplied by the superior quadrigeminate branches of both posterior cerebral arteries; bilateral disease of these trunks must be exceedingly rare; but, since the superior quadrigeminate artery supplies also the anterior corpus quadrigeminum, it seems probable that a lesion of that body may affect the pineal by cutting off some or all of its arterial supply—quite apart from pressure effects—and may thus modify its secretory processes. We may recall the case of Biancone, of tumour of the corpora quadrigemina, in which masturbation was a prominent feature: this has been connected causally with the pineal body by some writers. Be that as it may, the pineal body deserves a much closer and more conscientious histological study at the hands of neuro-pathologists than it has yet received; it may be much more often affected secondarily than we know at present: we may learn facts of value, if this be done. As to the origin and course of the sympathetic fibres which have been found by Cajal[46] and others in the pineal body, nothing definite appears to be known; one would suppose that they come from the inferior cervical sympathetic ganglion, by the vertebral plexus, along the basilar artery. There seems to be a promising field here for research, *e.g.*, the effect, if any, of extirpation of that ganglion, or stimulation, on the pineal body: it is conceivable that by such means the secretory activity of the pineal might be modified, in the case of young animals especially: one would like to know whether pinealine obtained after prolonged sympathetic stimulation, or extirpation, gave more or less than its usual effects on injection. I have dealt with the subject in section 5.

We come now to a very important subject which is a great stumbling-block to many writers, viz., the question of the pineal involution which occurs normally in childhood. Some writers seem to imply that, because a partial pineal involution occurs then, therefore the pineal has no function or functions after childhood. I look on this attitude as entirely erroneous. At the present time we have evidence which suggests that this involution begins somewhere about the age of 7 years in man, and ends normally at puberty. This means that there is (1) an early pineal function (prepuberal), which is active only in the first few years of life, in inhibiting premature sexual and genital development: a gradual involution occurs during the second half of prepuberal life, and by the time of puberty it is complete; those pineal elements, then, which subserve this prepuberal sexual function have now finished their work: they therefore undergo involution; we find evidence, then, of degeneration and disappearance of some pineal elements, together with a slight reduction in the size of the pineal body which later is still further reduced; (2) the other pineal function—which depends on those pineal elements that do not undergo involution at puberty—is active at any rate from puberty to extreme old age; we cannot, however, at present decide whether it begins only at puberty, for it may really be active from birth; nor do we know its function or functions. We have some evidence that pinealine from adult animals has the property of stimulating some unstriped muscles; but we cannot at present say anything definite about this non-sexual pineal function. Thus, it seems probable that of the two (or more) functions of the pineal body, one comes to an end normally at puberty, the other (or others) exists either from birth to death, or from puberty to death; of these the former is sexual, the latter at any rate not primarily sexual.

It is not yet possible to admit that Biach and Hulles[84] interpreted their own experimental findings wholly correctly; for their second figure, that of the pineal of a cat of 7 or 8 months of age, which had been castrated during the first few weeks of life, shows that, although many pineal elements have disappeared and the remaining parenchymal cells are a little smaller, and apparently less defined, than those of a normal cat's pineal, shown in Fig. 1, yet we are not entitled to say from this second figure that the atrophy of the pineal is anything like complete. We are not yet in a position to say whether, if these cats had been kept to extreme old age before the histological examination was made, their pineals would have shown a complete and total atrophy. This is the reason why I have urged, in the section dealing with needed experimental procedures, that it is essential that a histological examination should be made of the pineals of very old animals which had been castrated in very early life. The fact that the human pineal body appears to lessen in size after puberty —without disappearing—seems to point to the existence of at least two distinct functions, of which one normally finishes its work at puberty, and the other, whenever its work may have begun, goes on to the end of life.

Seigneur[6] has well said, in a burst of graduation eloquence: "The pineal gland, having known its days of glory, has fallen into neglect." At the same time we see signs on all sides that numerous active investigators are beginning to study the pineal in a more enlightened manner. The "rudimentary, useless" hypothesis has —unless I am greatly mistaken—gone for good. By the time this paper sees the light, we may have learnt from Foà what histological changes, if any, follow on pinealectomy in young chickens. We have to remember that the subject of pineal physiology is almost an untouched field of inquiry. In opening up new fields of inquiry, as in developing new countries, men always make some mistakes and miscalculations; and this is especially likely to occur in such a difficult subject as pineal physiology. In this review I have said but little on the obscure question of interglandular relationships. The most we can at present say, with any confidence, appears to be this: the pineal of young mammals and birds has (1) certainly a relationship with the development of the testes and, probably through them, with the secondary sexual characters and bodily growth; (2) probably a relationship with the pituitary, and the adrenal cortex; (3) possibly with the thyroid and thymus; (4) possibly with the ovaries: the experiments of Biach and Hulles[84] suggest it, whereas those of Foà[81] leave us in doubt—a doubt which may disappear when his histological studies shall be in our hands. [We shall probably learn before long from two physiologists, who are experimenting on certain aspects of pineal physiology which I have privately suggested to them, whether it is possible to induce an experimental hyperpinealismus by means of (1) pinealine from young animals, (2) pineal feeding, (3) pineal grafting.] It may quite well happen that embryonic pineal extracts may prove useful in teaching us more about the pineal body: the young science of experimental embryology has already gained many victories—especially in the hands of the brilliant school of American embryologists—and it undoubtedly has a future in front of it.

[Among the most generally useful papers on the pineal body may be mentioned: (1) "On the symptomatology of pineal tumours," Bailey and Jelliffe,[63] Münzer,[87] and Seigneur:[6] his thesis is excellent, but is weak on the experimental side; of these three writers, Münzer gives few references, whereas both Bailey and Jelliffe and also Seigneur give full references to all the recorded cases of pineal tumours; Seigneur gives references to as many as 65 cases in chapter 5 of his thesis;[6] it would be difficult to praise his industry too highly: he has even succeeded in finding my little letter on pineal experimentation,[88] which has naturally been overlooked by most recent writers on the pineal body owing to the fact that it was published in the correspondence columns of the *British Medical Journal*. (2) On the ancient history of the pineal body the papers by Faivre[2] (1857), Legros,[3] and Peytoureau.[4] (3) On the comparative anatomy and development, the papers by Studnicka,[5] Dendy,[16] Terry,[17] and Warren:[18] the postscript in Dendy's 1911 paper,[16] dealing with the work of Nowikoff (1910) in reptiles, is well worth study. (4) On the histology, the papers by Faivre[2] (1854), Dimitrova[50] (1901), Sarteschi[52] (1910), Krabbe[56] (1911), and Jordan[57] (1911). (5) On the experimental physiology, the papers by von Cyon[74] (1903), Dixon and Halliburton[75] (1909), Ott and Scott[76] (1911-12), Schäfer and Mackenzie[78] (1911), Sarteschi[52] (1910), Biach and Hulles[84] (1912), and, above all, Foà[81] (1912). I may add that I have not been able to refer to the paper on pineal cysts by F. Nassetti (*Riv. speriment. di Freniat.*, Vol. 38, 1912, p. 291), as it had not reached the library where I work when my MS. was sent in.]

7. Conclusions.

1. The facts of comparative anatomy, embryology, histology, clinico-pathology, and experimental physiology, point to the belief that the pineal body is functional in all those vertebrates which possess one.

2. The pineal body is a metamorphosed organ; not a rudimentary, useless, degenerated, degenerating, or disappearing organ; the phenomena, which have been urged in favour of the latter hypothesis, have been erroneously interpreted.

3. The pineal body probably furnishes an internal secretion; the crucial test for this may prove difficult of attainment; it has not yet been attempted.

4. So far as our at present imperfectly applied experimental studies have taught us, the pineal body of very young birds and mammals has an inhibitory action on the development of the testes and—probably through them—on bodily growth and the appearance of the secondary sexual characters.

5. A relationship of the pineal body with the ovaries is suggested by certain experiments,[84] but has not yet received confirmation from those of Foà[81] (1912).

6. A relationship with the pituitary and the adrenal cortex is probable, with the thyroid and thymus possible; but on these points nothing certain is yet known.

7. Histological studies, and also the most recent experiments of Ott and Scott[76] on adult pinealine (1912), seem to show that, in addition to its prepuberal-sexual function, the pineal body of man and other mammals has at least one other function; it is not primarily, at any rate, a sexual one; and it appears to be active either from puberty to the end of life, or from birth.

8. A true partial pineal involution begins normally in childhood at about the age of seven years, and is normally complete at puberty; its meaning is that the prepuberal sexual function of the pineal body has come to an end, and therefore involution occurs of those pineal elements which subserve that function.

9. The adult mammalian pineal body seems to have definite actions on some unstriped muscles (Ott and Scott especially), and it is functionally active normally up to the end of life.

10. The neuroglial and connective-tissue elements of the pineal body may have specific functions, quite apart from their purely mechanical rôle; but nothing definite is yet known on this matter.

11. The size of the pineal body bears no relation to the size of the brain or the size of the body.

12. The great variations of the pineal body—sometimes even in closely related forms—suggest that its functions vary, and are relatively greater in some than in others.

13. We are not yet in a position to say how the pineal body functionates.

14. The future of pineal physiology lies probably mainly in the hands of the experimental and chemical physiologist, to a less degree of the pathologist, and possibly to some extent of the experimental embryologist.

15. An exhaustive study of the many methods by which our present imperfect knowledge of comparative pineal physiology may be increased will be found in sections 5 and 6 of this paper.

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